REMARKS

Claims 1-24, 27-31, 33, 36, 38-40, 42-43 and 45-60, 62-63, 65-66 were pending. Claims 36, 38-40, 42-43, and 45-60 have been withdrawn from consideration. Claim 45 has been cancelled and claims 1, 14, 21-24, 27-31, 33, 38, 62-63 and 65-66 have been amended. New claim 67 has been added. Upon entry of the present amendment, claims 1-24, 27-31, 33, 62-63 and 65-67 will be pending and claims 36, 38-40, 42-43 and 46-60 will remain withdrawn.

Support for the amendments to the claims can be found throughout the specification and claims as originally filed. For example, support for the amendment to claim 1 reciting heteroaryl moieties can be found in paragraph [0096] of the application as filed. Support for the amendment to claims 1, 21-24, 27-31, 33, 62-63 and 65-66 (to recite a pharmaceutically acceptable salt or ester) can be found, for example, in paragraph [0124] of the application as filed. Support for the amendments to claims 14, 21-24, 27-31, 33 and 38 can be found, for example, in claims 1-2, 14, 21-24, 27-31, 33 and 38 as originally filed. No new matter has been added. Applicants reserve the right to pursue canceled subject matter in one or more continuation or divisional applications.

Election/Restrictions

Applicants respectfully reiterate the request for rejoinder of claims 36 and 45-60, as these claims are all dependent from claim 1 or claim 2 and all fall within the scope of elected group IV.

Applicants also respectfully reiterate that it is their understanding that, upon finding of an allowable product claim, method claims that depend from or otherwise include all the limitations of an allowable composition claim will be re-joined in accordance with the provisions of MPEP §821.04. Accordingly, Applicants respectfully request rejoinder of the claims of Group II, in pertinent part, should any of the pending composition claims be found to be allowable.

Claim Rejections - 35 U.S.C. §112

Claims 1-24, 27-31, 33, 62-63 and 65-66 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter of the invention. Specifically, claims 1 and 2 have been rejected for the use of the term "heteroaryl moiety" and claim 1 has been rejected for the use of the term "substituted." Applicants respectfully submit that claims 1 and 2 have been amended such that the above rejections have been rendered moot.

Claim 1 has also been rejected because the phrase "the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine" is "vague and indefinite because it is a hybrid claim containing the compound claim and the method of treatment." Applicants respectfully disagree and point out that Claim 1 is a *pharmaceutical composition* claim, not a compound claim. The MPEP clearly indicates that such "effective amount" language is appropriate in pharmaceutical composition claims. See, *e.g.*, MPEP §2173.05(c) III. Applicants, therefore, submit that a claim to a pharmaceutical composition which comprises a recited compound in an amount effective to provide a specified result is a proper composition claim. However, in the interest of expediting prosecution, claim 1 has been amended, as suggested by the Examiner, to remove the phrase "wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine." Support for this amendment to claim 1 can be found throughout the specification as originally filed, and at least in paragraph [0005] of the application as filed.

In view of the foregoing, Applicants respectfully request reconsideration of claims 1-24, 27-31, 33, 62-63 and 65-66 and withdrawal of the rejection under 35 U.S.C. 112, second paragraph.

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Claims 1-24, 27-31, 33, 62-63 and 65-66 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully submit that, in the interest of expediting prosecution, Claim 1 has been amended remove the phrase "wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine." Accordingly, the foregoing rejection has been rendered moot.

In view of the foregoing, Applicants respectfully request reconsideration of claims 1-24, 27-31, 33, 62-63 and 65-66 and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

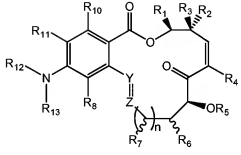
Double Patenting

Claims 1-24, 27-31, 33, 62-63 and 65-66 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22, 40, 43, 66 and 81 of co-pending U.S. Application No. 10/507,067.

Pursuant to MPEP 804(I)(B)(1), Applicants respectfully submit that, upon allowance of the present application, a terminal disclaimer will be filed, if appropriate, in co-pending U.S. Application No. 10/507,067, thus rendering a nonstatutory obviousness-type double patenting rejection moot.

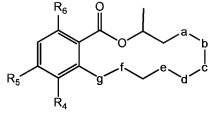
Claims Directed to Amine-substituted Macrolides (14-24, 27-31 and 33)

Applicants respectfully submit that claim 14, directed to compounds having the following structure:



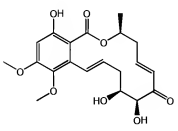
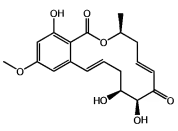
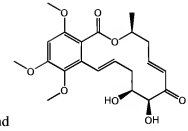
has been amended to independent format, and claims 21-24, 27-31 and 33 have been amended to depend from claim 14.

Applicants respectfully submit that claims 14-24, 27-31 and 33 were not subject to the rejection under 35 U.S.C. §103(a) (see below). Moreover, Applicants respectfully submit that Dreyfuss *et al.* does not render the compounds of claims 14-24, 27-31 and 33 obvious. At best, Dreyfuss *et al.* discloses compounds of the following formula:



wherein R_5 is OH, C_{1-4} alkoxy or C_{1-4} alkyl COO.

Exemplary compounds of Dreyfuss *et al.* include:

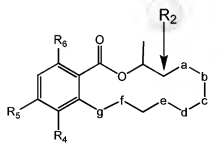


and

.

Dreyfuss *et al.* does not teach or suggest compounds of this formula wherein R_5 is an $-NR_{12}R_{13}$ group and wherein an alkyl group is substituted for the hydrogen at position R_2 on the macrocycle (see detailed discussion below). Applicants also submit that these claims are not subject to the rejections under 35 U.S.C. §112, at least for the reasons provided above in connection with claims 1 and 2.

In view of the foregoing, Applicants respectfully submit that claims 14-24, 27-31 and 33 are allowable, and request reconsideration of these claims.

Claim Rejections - 35 U.S.C. §103

Claims 1-3, 6-9, 11, 13, and 62 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dreyfuss *et al.* (EP 0606044). Applicants respectfully traverse this rejection, at least because Dreyfuss *et al.*, alone or in combination with the knowledge of a person of ordinary skill in the art at the time of filing, does not teach or suggest the placement of any group other than a hydrogen at position R_2 of the macrocycle (see figure below)



Moreover, there is no teaching or suggestion on the record of the reason why a person of ordinary skill in the art would modify the macrocycle of Dreyfuss *et al.* ***at position R_2.*** Not only does Dreyfuss *et al.* provide no teaching or suggestion of any resulting effect of replacing a hydrogen with an alkyl group, they also provide no teaching or suggestion that the particular hydrogen at position R_2 should be targeted for substitution. The Examiner argues that a person

of ordinary skill in the art would be motivated to make this substitution "in order to make the prior art compound more lipophilic..." However, prior to the teachings of the present invention, adding an alkyl group to the macrocycle in a specific position on the ring ***and*** in a specific stereochemistry would not have been obvious, at least because the synthetic preparation of such macrocyclic compounds is a complex multi-step process (see, *e.g.*, Dreyfuss *et al.*, pages 10-13 and the present application as filed, paragraphs [0204]-[1320]). Accordingly, even if a short chain alkyl would have a noticeable effect on the lipophilicity, there is no reason that a person of ordinary skill in the art would specifically choose position R_2 for substitution.

Moreover, Applicants have previously shown the unexpected properties of the compounds of the present invention in light of the prior art compounds. As the Examiner is aware, "[a] *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties." MPEP §2144.09 VII, citing *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967).

Applicants respectfully reiterate that the Declaration of John Wang (hereinafter "the Wang Declaration," filed August 16, 2006) demonstrates that the compounds of the present invention (*i.e.*, those with an alkyl at position R_2) unexpectedly have a significantly higher plasma stability than compounds with hydrogen at R_2 (see the Wang Declaration, paragraph 9). Applicants submit that a person of ordinary skill in the art at the time of filing of the present application could not have predicted that the replacement of a hydrogen with a C_1-C_6 alkyl group would have a significant increase in plasma stability.

In view of the foregoing, Applicants respectfully request reconsideration of claims 1-3, 6-9, 11, 13, and 62 and withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

The Examiner is invited to contact the undersigned with comments or questions regarding the present application.

Dated: October 24, 2008

Respectfully submitted,

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